REMARKS

The Office Action of May 21, 2010, presents the examination of claims 5-14. All of these claims remain pending.

Claims 5 and 14 are amended to recite that the methods "consist of" the steps enumerated. Editorial amendments that do not affect the scope of the claims are made to claims 7-10, 13 and 14. No new matter is added by any amendment.

The sole ground of rejection of claims 5-14 is under 35 USC § 103(a) for obviousness over Tobinick '195 in view of Bertini EP '276. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit again that the Examiner fails to establish *prima facie* obviousness of the claimed invention. In particular, the Examiner has considered the references in a piecemeal fashion, taking from them only their disclosure that supports his assertion of *prima facie* obviousness, and ignoring those parts of their disclosure that speak against obviousness of the present invention. This is an inappropriate approach to asserting obviousness, in that the Examiner is required to consider the references as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), citing *In re Kuderna*, 165 USPQ 575 (CCPA 1970).

The state of the art at the time the present invention was made

Questions of obviousness relate back to the time of making of the invention. 35 USC § 103. Applicants take a moment here to explain to the Examiner the state of the art at the time the present invention was made, especially with respect to defining what are IL-1, IL-8, TNF etc. and the roles they play in the inflammatory process, and particularly as they are involved in spinal cord injury (SCI).

Applicants enclose with this paper a number of references exemplary of the state of the art on interleukins and spinal cord injury at the time of filing the present application.

Exhibit 1, S.J. Hackett et al., *J. Med. Microbiol* 50:847-859 (2001), sets forth that a cytokine can be defined as a soluble molecule that mediates the interactions between virtually any cell lineages in an organism. (*See* page 847, second column, last line to page 848, left column, line 2.) In table 1, at page 847, this paper mentions as proinflammatory cytokines tumour necrosis factor α (TNF-α), Interleukin 1β (IL-1β), Interleukin 2 (IL-2), Interleukin-6 (IL-6) Interleukin-12 (IL-12), Leukemia leukocyte inhibitory factor (LIF).

In particular, interleukins are molecules specifically involved in signalling between cells of the immune system. These are generally cytokines that have had their amino acid structure determined (*see* Hackett et al., page 848, left column, line 2 and right column, line 1). As can be seen in Table I most of interleukins are in fact classified as cytokines.

Chemokines are molecules whose major function is chemoattraction (*see* Hackett et al., page 848, right column, lines 1-2). The aforementioned table 1 at page 847 classifies as chemokines Interleukin-8 (IL-8), RANTES, macrophage inflammatory protein -1-α (MIP-1-α), macrophage inflammatory protein -1-β (MIP-1-β), monocyte chemotactic protein -1 (MCP-1), and growth related gene product-α (GRO-α).

Exhibit 2 (C.A. Dinarello, *Chest* 118:503-508 (2000)) presents in the following flow sheet (taken from Figure 1) the reactions implicated in the inflammatory process and the roles exercised in the same by proinflammatory cytokines and chemokines.

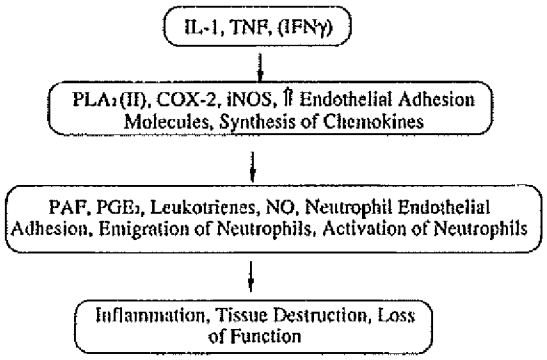

FIGURE 1. The inflammatory cascade triggered by IL-1 and TNF. iNOS = inducible NO synthase; PAF = platelet-activating factor.

As clearly evidenced in this figure and also at page 504 right column lines 29-32, **whether induced by an infection, trauma, ischemia, immune activated T-cells or toxins**, IL-1 and TNF are the cytokines that initiate the cascade of inflammatory mediators by targeting the endothelium and triggering in the successive step among other reactions also the synthesis of chemokines and among them, IL-8, which is a neutrophil chemoattractant. These chemokines, in the successive step, activate neutrophils to degranulate which, in the last step, triggers tissue damage (*see* Dinarello, page 504, right column, lines 13-16).

Consequently, from the above common general knowledge, it is clear that IL-1 is an interleukin much more powerful than IL-8, as it is one of the pro-inflammatory cytokines originating the whole inflammatory process. On the contrary, IL-8 is a downstream effector of IL-1 /TNF and has a **more specific and limited role** in the inflammation process, namely chemotaxis.

At the time the present invention was made, many prior art studies identified a key role of the proinflammatory cytokines such as IL-1, TNF or IL-6 in spinal cord injury, especially in the early stage of the injury. Applicants submit, as **Exhibit 3,** the abstracts of the most significant studies evidencing this aspect. In addition, Applicants wish to stress that abstracts 2 and 3 of Exhibit 3 also teach that TNF and/or IL-1 play a **key role** in apoptosis; and especially abstract 3 evidencing that administration of IL-1 receptor antagonist completely abolished the increase in contusion induced apoptosis and caspase 3-activity.

As a further confirmation of the key role exerted by the aforementioned pro-inflammatory cytokines in SCI, Applicants submit **Exhibit 4**, J.Z. Pan et al., *J. Neurosci. Res.* 68:315-322 (2002), suggesting that the appearance of increased levels of cytokine mRNAs (IL-1-α, IL-1-β, TNF- α and IL-6), beginning as early as 15 minutes following SCI, supports a prior stimulation by cytokines or other inflammatory signals. Because cytokine mRNAs are not themselves bioactive and they are commonly produced in response to active cytokines, SCI stimulates the nearly immediate release of stored cytokines and the induction of cytokine mRNAs (*see* page 321, left column line 9 to right column, line 7).

Therefore, at the time the invention was made, in view of the above discussed prior art that teaches the involvement of IL-1 and TNF as the key pro-inflammatory cytokines responsible for the inflammatory process as well as for the neurological damage in SCI, the skilled person would have been motivated to think that the sole agents able to effectively treat an inflammatory process like that involved in spinal cord injury were IL-1, or TNF receptor inhibitors, able therefore to block **"ab initio"** the inflammatory process cascade.

Consequently, at the effective filing date of the present application, the state of the art and the scientific literature on SCI and cytokines would have taught the skilled person away from the claimed invention, which is a therapeutic method wherein inhibitors of IL-8 induced chemotaxis of polymorphonuclear lymphocytes, such as the compounds of formula (I), are administered **as the sole active ingredient** for the treatment of SCI, so as to counter the effects of PMN chemotaxis such as tissue damage and loss and apoptosis. In fact, as discussed above, at the time the invention was made, the general knowledge was that:

- Proinflammatory cytokines trigger the inflammatory process, and the sole hypothesized drug for treating this condition was the administration of antagonist of pro-inflammatory cytokine receptors,
- chemokines are only a part of many substances produced in the second reaction step of the inflammatory pathway,
- IL-8 is only one of the several possible chemokines produced during the inflammatory process.

In view of the above-described state of the art, Applicants now turn to addressing the references cited by the Examiner.

In the context of the above described state of the art, Tobinick does not provide any teaching that could take away the above prejudice in the prior art and suggest to the skilled man the invention as presently claimed.

In fact, as stated in the specification of the present Application (*see* page 3 lines 17-21), Tobinick intends "*the treatment of a number of different pathologies, including SCI by means of antagonists of IL-1, IL-6 and IL-8*".

Tobinick mentions IL-8 among the cytokines whose inhibition would be advantageous for the treatment of a number of neurological disorders listed in the patent application. However, the citation of this interleukin is merely in passing and the patent application is substantially directed to the role of IL-1 and TNF in these pathologies. Although IL-8 is mentioned, its role in the disorders addressed by Tobinick is never discussed.

In particular, at paragraph [0052] Tobinick recites that IL-1 is a proinflammatory cytokine that has been implicated in the inflammatory response occurring, among other sites, also in the spinal cord and, in the same paragraph merely affirms that IL-8 and IL-6 are both pro-inflammatory cytokines, like IL-1.

In the above description of the state of the art, as evidenced by Hackett et al., Applicants have pointed out that IL-1 is a potent pro-inflammatory cytokine, whereas IL-8 is only one type of chemokine produced in the second phase of the inflammatory process. Consequently, first the aforementioned Tobinick assertion is **not** scientifically correct; to the contrary IL-8 is **not** recognized in the art as being a pro-inflammatory cytokine.

In addition, Tobinick only mentions IL-8 as a cytokine involved in inflammatory responses in neurological disorders, but never asserts or demonstrates that an IL-8 antagonist may be advantageously used in the treatment of SCI. There is simply not any indication of this concept at all in Tobinick.

The only experimental evidence present in Tobinick relates to the treatment of a pathology different from SCI (Acute Lumbar Radiculopathy) with **a TNF antagonist** (Etanercept *see* Tobinick [0037]).

In the absence of a clear indication and of experimental data attesting the efficacy of IL-8 inhibitors/antagonists in SCI, the skilled man, aware of the primary importance role showed by

pro-inflammatory cytokines in the SCI process, as compared to the chemokine role played by IL-8, would not have seriously contemplated using IL-8 inhibitors, **as the sole active ingredients,** for the treatment of SCI.

In this regard, Applicants submit that the above belief of the skilled person is indeed corroborated by Tobinick. In fact, when discussing specifically the treatment of SCI (*see* [0068]), Tobinick again teaches to use as the active ingredient etanercept, **which is a TNF antagonist** (*see* Tobinick [0037]) and does not mention any IL-8 antagonist.

In addition in the same paragraph [0037] **no** active ingredient having inhibitory activity of chemotaxis is cited, but only IL-1 and TNF receptor antagonists.

In other words, Tobinick in fact points in the same direction as that of the prior art studies mentioned in Exhibit 3 and Exhibit 4, suggesting that the sole effective treatment of spinal cord injury (but also of other pathologies) involves the use of antagonists of receptors of the potent pro-inflammatory cytokines.

In view of the foregoing, from the confusing and contradictory teaching of Tobinick, the skilled person would **not** have gained any valid hint addressing him towards the therapeutic method as presently claimed, consisting of the administration of inhibitors of polymorphonuclear leuckocyte chemotaxis induced by IL-8.

As pointed out in Applicants' previous reply, Bertini et al, at [0016] and [0045], only state that the N(2-arylpropionyl)sulphonamides, namely the same compounds used in the method as claimed in claim 5, are characterized by the capability of inhibiting *in vitro* the chemotaxis of PMN human leukocytes stimulated by IL-8 .

At [0048] and in claim 9 of Bertini et al., the diseases listed as having a mechanism involving PMN chemotaxis are only psoriasis, rheumatoid arthritits, ulcerative cholitis, acute respiratory insufficiency idiopathic fibrosis, glomerulonephritis. Spinal cord injury is however not encompassed.

Thus, the combination of Bertini et al. with Tobinick does not remedy the deficiencies of Tobinick in failing to establish any expectation of success in making the present invention.

Applicants stress that, **unlike Tobinick**, they have submitted ***in vivo*** experimental data that attest to the **real** effectiveness of the compounds of formula (I) in the treatment of SCI and related effects.

Applicants submit that the scientific evidence and arguments presented herein clearly demonstrate that the invention as presently claimed is not obvious over the combination of Tobinick and Bertini. Accordingly, the instant rejection should be withdrawn.

Applicants believe the pending claims are in condition for allowance, and such favorable action is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachments: Exhibits 1-4